Main Submission

Getting 'JAK'ed about PI3K signaling in metastatic colorectal cancer

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Colorectal cancer (CRC) is an increasingly common malignancy with approximately 9,100 deaths and 22,500 diagnoses having occurred in 2010 in Canada alone[1]. While new methods of detection, diagnosis and prevention are being developed, metastatic colorectal cancer (mCRC) still reduces 5-year survival to less than 10%[2]. Treatment options for CRC include surgery, radiation therapy, chemotherapy and monoclonal antibody therapy. Cetuximab, a chimeric monoclonal antibody, acts to inhibit the epidermal growth factor receptor (EGFR) and is approved for treatment of CRC[3,4]. Cetuximab binds EGFR, inhibiting the interaction between the epidermal growth factor (EGF) ligand and receptor. The EGF-EGFR interaction is known to lead to activation of intracellular effectors, including Kirsten rat sarcoma viral oncogene homolog (*KRAS*), serine/threonine-protein kinase B-Raf (*BRAF*), phosphatidylinositol-3-kinase catalytic alpha polypeptide (*PI3KCA*) and potentially other unidentified proteins[5,6,7,8]. Together, these proteins are part of an 'interactome' involving multiple layers of signaling and protein-protein interactions responsible for cell proliferation, growth, survival and motility[7].

EGFR expression is apparent in 30-85% of CRC patient tumours and has been linked to reduced survival[9]. Therefore, when considering cetuximab as a treatment regimen, it is important to understand whether downstream mutations at the intracellular level would impact the efficacy of the treatment. When *KRAS*, *BRAF* and *PI3KCA* are mutated, signaling through RAS-RAF and PI3KCA pathways goes unchecked and treatment using EGFR inhibitors would yield no results. As cell signaling spirals out of control, the normal cellular environment is now out of balance, which can lead to cancer development. This observation was made especially clear when Lievre *et al*. discovered that patients with a *KRAS* mutation were refractory to cetuximab therapy[10]. This is an important finding as 30-40% of non-responding patients will have this mutation[10]. Furthermore, studies have shown that a wildtype *BRAF* gene is necessary for response to cetuximab[8]. Lastly, *in vitro* evidence shows that cells with mutant *PI3KCA* and loss of the phosphatase and tensin homolog (*PTEN*) gene are more resistant to cetuximab therapy as would be expected since PTEN negatively regulates PI3KCA signaling[11]. However, before all of this was known, cetuximab therapy was prescribed to patients who had previously failed other treatment regimens, including single dose chemotherapy/combination therapy. When combination therapy fluorouracil and irinotecan (FOLFIRI) or fluorouracil and oxaliplatin (FOLFOX) was coupled to cetuximab treatments, increases in progression-free survival and overall survival were observed[9,10,12]. Therefore, the importance of EGF-EGFR signaling in CRC and mCRC is apparent; however to what extent it is responsible for disease is still a contentious issue.

Mutations in downstream effectors of EGFR signaling are likely responsible for varying phenotypes in CRC, as anti-EGFR therapies work in patients who overexpress EGFR without these mutations[10]. These observations have lasting implications to the treatment field because patients can be grouped into subpopulations that can be treated effectively using cetuximab, while sparing others from indirect toxicity and financial burdens. The downstream targets of EGF-EGFR signaling, RAS-RAF and PI3KCA, are the molecules that need further understanding as the current literature does not seem to account for the differences in patient response to cetuximab. Determining *PI3KCA-PTEN* mutation status in patient tumours is important to identify whether there is increased signaling through the AKT pathway, a downstream effector of PI3KCA signaling involved in cellular survival signals and angiogenesis, just as

determining the *KRAS* and *BRAF* status is also relevant.

Overall, when we consider this intertwined 'interactome', it is important not to discount the ability of other unmentioned players as having a role in pathogenesis. The JAK-STAT pathway has direct effects on PI3KCA signaling, and in normal cellular physiology, is important in transducing cytokine-mediated signaling[13]. JAK-STAT signaling could therefore have an important influence on the AKT pathway through PI3KCA signaling, resulting in increased cell survival and angiogenesis[13]. It has been shown that patients with mutated, constitutively active PI3KCA are refractory to cetuximab therapy, which may also be a consequence of JAK activity on PI3KCA[13]. *In vitro* evidence corroborates this theory, as JAK inhibition is linked to an increase in apoptosis and decreased cellular invasion by CRC cells[14].

With such a convoluted series of signaling pathways involved in CRC pathogenesis, further basic molecular research is of utmost importance. The best therapeutic approach appears to be stratifying patients based on *PTEN*, *KRAS*, *BRAF*, *PI3KCA* and possibly *JAK-STAT* mutation/expression status of the patient's primary tumour. Of course this calls into question whether or not the metastatic sites have remained genetically similar to the primary tumour, however this discussion is beyond the scope of this article.

Although stratifying all mCRC patients based on mutational status is extremely arduous with respect to cost and decreased quality of life, it is not nearly as expensive as non-specific treatment regimens. Therefore, it is only once these patients are treated accordingly that the medical community will achieve higher levels of treatment response in patients suffering from metastatic colorectal cancer.

References

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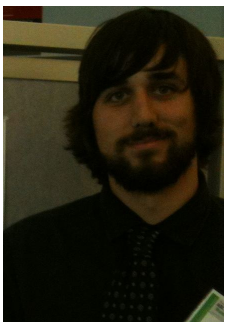

Author Profile

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